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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,331	03/29/2004	Bill J. Peck	10031531-1	5115

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	

NOTIFICATION DATE	DELIVERY MODE
12/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,331	PECK ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-28* is/are pending in the application.

4a) Of the above claim(s) *17-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-16 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/25/2007 has been entered. Claim 1 has been amended. Claims 3 and 25 are cancelled. Claims 1, 2, 4-24 and 26-28 are pending. Claims 17-24 and 26-27 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 2 and 4-16 and 28 are withdrawn from consideration as being drawn to a non-elected invention.

Previous Rejection

2. The prior art rejections under 35 USC 103(a) as being unpatentable over Anderson et al in view of Schleifer (A) or Schleifer (B) is maintained and discussed below. The prior art rejection under 35 USC 103(a) as being unpatentable over Anderson et al in view of Schleifer (A), Schleifer (B) and further in view of Blanchard et al is maintained and discussed below.

Claim Rejections - 35 USC § 103

3. Claims 1, 2, 4-15 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (citation made of record in previous office action) in view of in view of Schleifer (A) {U.S. Patent No. 6,077,674, issued 20 June 2000) or Schleifer (B) (U.S. Patent No. 6,309,828, issued 30 October 2001).

Regarding claims 1, Anderson et al disclose the method comprising contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface. Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step (i) of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et

al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20); removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al further teach the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

While the reference does not use the term "array", the term is defined by dictionary.reference.com as "a larger group, number or quantity of people or things". Anderson et al teach production of a plurality of oligonucleotides attached to cpg substrate ("1. Oligonucleotide Synthesis", Columns 19-22 and Column 24, lines 5-35). Anderson et al further teach wherein the polymers are cleaved from the support for subsequent use and/or immobilization (col. 14 and col. 20, lines 10-25, e.g., hybridization to oligonucleotides immobilized on solid supports (col. 20, lines 20-21). While this teaching suggest that the polymers are subsequently immobilized, Anderson et al do not expressly teach the production of addressable array. However, polymer synthesis on cpg supports followed by polymer cleavage for the production of an addressable array was well known and routinely practice in the art at the time the claimed invention was made as taught by Schleifer (A) and (B).

In a method similar to that of Anderson et al, Schleifer (A) teaches method steps of polymer synthesis comprising repeated monomer additions to cpg supports (col. 9, lines 6-10), cleavage of the polymers from the supports (col. 10, lines 10-15) and immobilization of the polymers to feature locations on the array (col. 10, lines 37-42) whereby "costly and time consuming purification steps" is avoided while providing a high purity full length oligonucleotide array (col. 10, lines 47-51).

Schleifer (B) teaches a similar method of polymer synthesis comprising repeated monomer additions to cpg supports, cleavage of the polymers from the supports and immobilization of the polymers to feature locations on the array (col. 9, line 22 to col. 10, line 30 and Example 3) whereby an addressable array is produced (see definition of an array, col. 1, lines 13-15). Schleifer (B) teaches this polymer synthesis coupled to array production is an efficient, cost effective method of spatially integrating polymer synthesis and replicate array fabrication (abstract and col. 2, lines 22-31).

It would have been obvious to one or ordinary skill in the art at the time the claimed invention was made to apply the polymers synthesized by Anderson et al to the further step of addressable array fabrication taught by Schleifer (A) and/or (B). One of ordinary skill in the art at the time of the claimed invention would have been motivated to do so based on the well known practice of addressable immobilization of pre synthesized polymers as taught by Schleifer (A) and (B). One of ordinary skill in the art would have been further motivated to do for the expected benefits of producing replicate arrays via efficient cost-effective methods of spatially integrating polymer synthesis and array fabrication as suggested by Schleifer (B) (abstract, col. 2, lines 22-31) and for the further benefits of providing high purity full-length oligonucleotides while avoiding costly and time consuming purification steps as suggested by Schleifer (A) (col. 10, lines 47-51).

Alternatively, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to apply the deblocking fluid synthesis steps of Anderson et al to the polymer synthesis of either Schleifer (A) or (B). Anderson et al teach polymer synthesis in particulate beds is problematic in that fluid flows through the bed is non-uniform resulting in non-uniform reactions and hence inefficient and inaccurate polymer synthesis (col. 1-4). Anderson et al further teach that their method of precise fluid control through the particle bed minimizes the problems of micro- and macro-anomalous flow provides precise and efficient polymer synthesis (col. 5 and 6). Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to apply the precisely controlled fluid flow of Anderson et al to the particle bed synthesis of Schleifer (A) and/or (B) for the expected benefit of precise and efficient polymer synthesis while eliminating the problems inherent in particle bed synthesis as taught by Anderson et al (col. 1-6).

Regarding Claims 2, Anderson et al disclose the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14).

Regarding claims 4, Anderson et al wherein the washing fluid has a density that is lower than the density of the deblocking fluid (Column 5, lines 3-38 and Column 6, lines 13-36). In one embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

Regarding Claim 5, Anderson et al disclose wherein the wash is a low viscosity (see col. 7, lines 68 to col. 8, line 1 and Table II, step 3 with discloses that the wash solution is acetonitrile).

Regarding claim 6 and 8, Anderson et al discloses wherein the wash fluid is acetronitrile (column 13, line 67-column 14, line 1), which has a low viscosity (col. 7, line 68 to col. 8, line 1). It is commonly known in the art base standard physical data that acetonitrile has a viscosity of 0.38 cp. Therefore, it is an inherent property that the wash fluid (acetonitrile) has a viscosity that does not exceed about 1.2 cP.

Regarding claim 7, Anderson et al disclose wherein said wash fluid is an organic fluid (Table II, step 3).

Regarding Claim 9, Anderson et al disclose the method wherein displacing comprises flowing the subsequent liquid across the surface to produce a stratified liquid interface that moves across the surface (Column 12, lines 28-67 and Fig. 2A-2D).

Regarding Claim 10, Anderson et al disclose a method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on control pore glass, the two different sequences being e.g. product and failed sequences, Column 20, lines 10-25) as previously discussed above. Anderson et al further teach the method wherein the steps are performed in a flow cell wherein the flow rate is controlled and monitored during passage of reagents (Column 5,lines 25-27; Column 14, lines 44-53 21). Anderson et al teach that it is important to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (Column 21, lines 30-65) but they are silent regarding specific flow rates. However, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the flow rate during the synthesis steps of Anderson to obtain optimal flow rates (e.g. about 1-20 cm/x). One of

ordinary skill in the art would have been motivated to adjust the flow rate so as to maximize syntheses reaction with minimal waste of reagents as desired by Anderson et al (Column 21, lines 30-65).

Regarding Claim 11, Anderson et al teach wherein the method comprises a sensing movement (rotation) that moves a stratified interface across the surface (column 12, lines 28-67 and Fig. 2A-2D).

Regarding Claim 12-14, Anderson et al disclose the method wherein the steps are preformed in a flow cell i.e. internal space for fluid flow so as to contact solid support (Column 5, lines 20-38).

Regarding Claim 15, Anderson et al disclose the method wherein said surface is contacted with a capping liquid prior to said deblocking (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

Regarding claim 28, Anderson et al teach wherein the substrate is a planar substrate, e.g., flat disc (col. 6, lines 49-52).

Therefore, Anderson et al meets the limitation of the claims noted above.

Claim Rejections - 35 USC § 103

4. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al Schleifer (A) and Schleifer (b) and further in view of Blanchard (citation made of record in prior Office Action).

Regarding Claim 16, Anderson et al in view of Schleifer (A) and Schleifer (B) disclose the method of claim 1 further comprising contacting a blocked monomer at first and second locations having functional groups (e.g. supports having the first monomer attached, (see Anderson, column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface as previously discussed above.

Anderson et al in view of Schleifer (A) and Schleifer (B) do not teach monomers addition using a pulse-jet. However, pulse-jet addition of monomers during multi-step synthesis of polymers was well known in the art at the time the claimed invention was made as taught by Blanchard.

Blanchard teaches a similar method of oligonucleotide synthesis on a solid support wherein the support is placed in a flow cell for all reaction except for monomer addition (Column 4, lines 3-22). Blanchard teach the monomer addition using a pulse jet provides precise, discrete and small volumes of monomer are added to a support (Column 5, lines 41-56) whereby multiple and different monomers dispensed simultaneously thereby greatly reducing the time of array synthesis (Column 11, lines 48-61).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the pulse-jet dispenser of Blanchard to the monomer addition step of Anderson et al. One of ordinary skill in the art would have been motivated to do so for the expected benefit of simultaneously providing multiple and different monomers precisely at, discrete and small locations on to the support (e.g. membrane/disc) of Anderson et al with greatly reduced time of array synthesis as taught by Blanchard (Column 5, lines 41-56 and Column 11, lines 48-61).

Response to Arguments

5. Applicant traverses the rejection on the grounds that the new limitation at step (e) wherein the steps (a to (d) are reiterated at least once to produce said addressable array having a first polymeric ligand at said first location of said substrate and a second polymeric ligand at said second location of said substrate is not taught by the cited references. Applicant states that the Examiner's rejection is based on the assumption that the claims read on a method in which polymers are presynthesized and then deposited at specific locations to produce an addressable array. Applicant states that the claims are directed to an in situ fabrication process in which an addressable array is produced by synthesizing nucleic acid ligands directly on the surface of a solid support in a manner that sequentially adds the monomeric units one at a time. Applicant states

that Anderson et al does not teach or suggest the in situ production of an addressable array of at least two nucleic acid polymeric ligands. Applicant further contends that since Schleifer (A) and Schleifer (B) were cited for the purpose of an alleged teaching of making an addressable array by depositing premade polymers onto a surface of a support. Applicant states that in regards to claim 16, Blanchard fails to make up for the deficiency between Anderson et al in view of Schleifer (A) and Schleifer (B) in the present case.

6. All of the arguments have been thoroughly reviewed and considered but are not found persuasive. In response to Applicant's arguments that the cited prior art does not teach the instant invention because the cited prior art teaches wherein polymers are presynthesized and then deposited at specific locations to produce an addressable array, it is noted that the reference is based on an obviousness-type rejection and not a rejection based on anticipation. MPEP states that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Anderson et al provides producing a solid surface comprising a first and second polymer ligand produced on a solid surface. As stated in the prior Office action, Anderson does not teach that the solid surface is an addressable array. The secondary reference of Schleifer (A) and (B) provides this teaching and provides motivation for spatially integrating the polymer synthesized by Anderson with the addressable array fabrication as suggested by Schleifers (A) and (B). Further, contrary to Applicant's arguments,

MPEP states that obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The combination of Anderson et al in view of Schleifer (A) and (B) provides the claims as currently amended.

7. In response to Applicant's arguments that the claims are directed to an in *situ* fabrication process in which an addressable array is produced in a manner that sequentially adds the monomeric units one at a time, it is noted that the claims do not recited the limitations argued by applicant. The decision of the court in *In re Bigio*, 72 USPQ2d 1209 (Fed. Cir. 2004) strongly supports the breadth of interpretation. The court noted that "[T]his court counsels the PTP to avoid the temptation to limit broad claim terms solely on the basis of specification passages". In concert with *Bigio* is the decision in In re American Academy of Science Tech Center, 70 USPQ2d 1827, 1834, 1834 (Fed. Cir. 2004), where the Federal Circuit noted, "We have cautioned against reading limitations into a claim from the preferred embodiment described in the specification, even if it is the only embodiment described, absent clear disclaimer in the specification". Further MPEP states that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In this case, the claims the do not recited that the an *in situ* fabrication process or wherein a sequential

addition of monomeric unit are performed. The claims on require that a first polymeric ligand and a second polymeric ligand be produce at a first location and a second location of an addressable array. The cited references meet these limitations.

In response to Applicant's arguments further concerning sequential order of the method steps, it is noted that MPEP 2144.04 notes "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results". The rejection to the claim 16 is maintained for the same reasons discussed above. Applicant's amendment and arguments are not sufficient to overcome the prior art rejections.

New Ground(s) of Rejections

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 16 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Bass (US 6,420,180 B1, July 16, 2002). Regarding claim 1, Bass teaches a method of producing an addressable array of at least two different nucleic acid ligands covalently bonded to a surface of a substrate, said method comprising: (a) contacting blocked nucleoside monomers to at least a first location and a second location of a substrate surface displaying functional groups under conditions sufficient for said .blocked

nucleoside monomers to covalently bond to said surface in said first and second locations to produce a substrate surface displaying covalently bound blocked monomers; (b) contacting said surface displaying blocked nucleoside monomers with an oxidation fluid to produce an oxidized surface; (c) contacting said oxidized surface with a deblocking fluid {deprotecting fluid}; (d) removing deblocking fluid from said deblocked surface by displacing said deblocking fluid from said surface with a wash fluid; and (e) reiterating steps (a) to (d) at least once to produce said addressable array having a first polymeric ligand at said first location of said substrate and a second polymeric ligand at said second location of said substrate (col. 1. line 55 to col. 2, lines 1-9 and 28-34 and Figures 1-3, which is identical to the Figures 1-3 of the instant invention).

Regarding claim 16, Bass et al teach the method of claim 1, wherein said blocked nucleoside monomers are contacted with said surface by pulse-jet deposition (col. 3, lines 61-67 and col. 7, lines 35-38).

Regarding claim 28, Bass et al teach the method according to claim 1, wherein said substrate is planar (col. 13, lines 2-5).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 2, 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bass as previously applied above in view of Anderson et al as previously applied in the previous Office action.

Regarding claims, Bass et al teach a method of producing an addressable array of at least two different nucleic acid ligands covalently bonded to a surface of a substrate, said method comprising contacting blocked nucleoside monomers to at least a first location and a second location of a substrate surface displaying functional groups under conditions sufficient for said .blocked nucleoside monomers to covalently bond to said surface in said first and second locations to produce a substrate surface displaying covalently bound blocked monomers; (b) contacting said surface displaying blocked nucleoside monomers with an oxidation fluid to produce an oxidized surface; (c) contacting said oxidized surface with a deblocking fluid; (d) removing deblocking fluid from said deblocked surface by displacing said deblocking fluid from said surface with a wash fluid; and (e) reiterating steps (a) to (d) at least once to produce said addressable

array having a first polymeric ligand at said first location of said substrate and a second polymeric ligand at said second location of said substrate (col. 1. line 55 to col. 2, lines 1-9 and 28-34 and Figures 1-3, which is identical to the Figures 1-3 of the instant invention).

Bass does not provide any additional information on the wash fluid or deblocking fluid or wherein the method utilizes a flow cell.

Anderson et al disclose the method similar to that of Bass comprising contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface. Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step (i) of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20); removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al further teach the method wherein the solid

supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

With respect to claim 2, Anderson et al disclose the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14).

With respect to claim 4, Anderson et al wherein the washing fluid has a density that is lower than the density of the deblocking fluid (Column 5, lines 3-38 and Column 6, lines 13-36). In one embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

With respect to claim 5, Anderson et al disclose wherein the wash is a low viscosity (see col. 7, lines 68 to col. 8, line 1 and Table II, step 3 with discloses that the wash solution is acetonitrile).

With respect to claims 6 and 8, Anderson et al discloses wherein the wash fluid is acetronitrile (column 13, line 67-column 14, line 1), which has a low viscosity (col. 7, line 68 to col. 8, line 1). It is commonly known in the art base standard physical data that

acetonitrile has a viscosity of 0.38 cp. Therefore, it is an inherent property that the wash fluid (acetonitrile) has a viscosity that does not exceed about 1.2 cP.

With respect to claim 7, Anderson et al disclose wherein said wash fluid is an organic fluid (Table II, step 3).

With respect to claim 9, Anderson et al disclose the method wherein displacing comprises flowing the subsequent liquid across the surface to produce a stratified liquid interface that moves across the surface (Column 12, lines 28-67 and Fig. 2A-2D).

With respect to claim 10, Anderson et al disclose a method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on control pore glass, the two different sequences being e.g. product and failed sequences, Column 20, lines 10-25) as previously discussed above. Anderson et al further teach the method wherein the steps are performed in a flow cell wherein the flow rate is controlled and monitored during passage of reagents (Column 5,lines 25-27; Column 14, lines 44-53 21). Anderson et al teach that it is important to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (Column 21, lines 30-65) but they are silent regarding specific flow rates. However, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the flow rate during the synthesis steps of Anderson to obtain optimal flow rates (e.g. about 1-20 cm/x). One of ordinary skill in the art would have been motivated to adjust the flow rate so as to maximize syntheses

reaction with minimal waste of reagents as desired by Anderson et al (Column 21, lines 30-65).

With respect to claim 11, Anderson et al teach wherein the method comprises a sensing movement (rotation) that moves a stratified interface across the surface (column 12, lines 28-67 and Fig. 2A-2D).

With respect to claim 12-14, Anderson et al disclose the method wherein the steps are preformed in a flow cell i.e. internal space for fluid flow so as to contact solid support (Column 5, lines 20-38).

With respect to claim 15, Anderson et al disclose the method wherein said surface is contacted with a capping liquid prior to said deblocking (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

The claims 2 and 4-15 merely recite a plethora of manipulation reagents and methodologies, as well as routine optimization or reaction components, concentrations, and parameters. Clearly such conventional and trivial modification and optimizations do not contribute towards patentability. Thus, one of ordinary skill in the art would have been motivated to modify the method of Bass et al with the reagents of Anderson in the manner of the claims to achieve the expected benefits, optimizations an/or expanded applications. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods with a reasonable expectation of success.

Conclusion

12. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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